REMARKS

Claims 1-82 are pending in the present application. Claims 20, 25, 28, 43-44, 48, 59-60, 62-63 and 74-79 are rejected under 35 U.S.C. 102(e). Claims 20-82 are rejected under 35 U.S.C. 103(a). Claims 1-82 are rejected under the judicially created doctrine of obviousness-type double patenting. Applicants respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of the amendments and remarks below.

The Invention

The present invention provides novel condensation drug aerosols and methods for producing such aerosols. These condensations aerosols have little or no pyrolysis degradation products. The unique method for generating or producing such aerosols employs rapid vaporization of the drug to minimize drug degradation during the process. These vaporized drugs are subsequently condensed to form particles of a desirable particle size for inhalation. These aerosols are especially useful in the treatment of acute or chronic conditions wherein rapid onset of treatment is desirable.

The Interview

An interview was conducted on August 4, 2005. The participants were Examiners Haghighatian and Kunz, applicant's representatives William L. Leschensky and Barry J. Swanson and inventor Joshua D. Rabinowitz. Applicant's representatives thank the Examiner for the courtesy extended in the interview. The interview began with a general discussion of the present application with respect to the other currently pending applications owned by Alexza Molecular Delivery Corporation. Dr. Rabinowitz provided a detailed scientific discussion of the prior art cited by the Examiner the Office Action dated March 8, 2005 as in the context of the present invention. Applicant presented arguments that the present invention is not obvious over the cited art and proposed amendments that could be made to place the claims in condition for allowance. While no agreement was reached at the interview with respect to every aspect of the rejection, Examiner Haghighatian indicated that certain proposed amendments to the kit claims would appear to place the claims in condition for allowance.

The Amendments to the Claims

Without prejudice to the Applicants' rights to present claims of equal scope in a timely filed continuing application, to expedite prosecution and issuance of the application, the Applicants have amended Claims 1, 4, 6-15, 18, 74-76 and 80 and cancelled Claims 20-73 and 77. The Applicants also have presented new Claims 83-95. The amended claims and the new claims are supported by the

specification (including, U.S. provisional application Ser. No. 60/317,479 at page 5, lines 17-19 and page 30, lines 25-27, incorporated by reference in its entirety).

The amendments to the claims do not introduce new matter. Applicants respectfully submit that the amendments to the claims put the case in condition for allowance. The Examiner is respectfully requested to enter the amendments to the claims and allow all amended claims.

The Rejection under 35 U.S.C. §102(e)

The Examiner rejected Claims 20, 25, 28, 43-44, 48, 59-60, 62-63 and 74-79 under 35 U.S.C. §102(e) as being anticipated by Bryon et al. (20040016427 A1). In support of this rejection, the Office Action states that "Byron et al. disclose a method and apparatus for generating an aerosol . . . formed by supplying a material in liquid form to a tube and heating the tube such that the material volatizes and expands out of an open end of the tube." Office Action at 2. The Office Action goes on to state that the volatized material combines with ambient air such that the volatized material condenses to form the aerosol and that the aerosols are intended for inhalation and typically have a mass median particle diameter of less than 2 microns.

In order to expedite the prosecution, Applicants have cancelled claims 20-73 and 77 and amended Claim 74. As amended, Claim 74 is directed to kit for delivering a condensation aerosol. In accordance with the invention, the kit comprises a thin film of a drug composition comprising a drug, on a solid support, and a device for providing the condensation aerosol. The condensation aerosol is formed by heating the drug composition to produce a vapor, and condensing the vapor to form a condensation aerosol comprising the drug. The condensation aerosol comprises particles characterized by less than 10% drug degradation products by weight, and has an MMAD of less than 5 microns. Furthermore, the drug is a heat stable drug. Support for this amendment is found throughout the specification and as noted above.

Byron et al. fails to teach or disclose a thin film of a drug composition comprising a drug, on a solid support, or heating such a drug composition to produce a vapor. Furthermore, Byron et al. lacks specific disclosure on a heat stable drug or a condensation aerosol comprising particles characterized by less than 10% drug degradation products as those terms are used with respect to the present invention. See, e.g., Paragraph [0096] ("'Drug degradation product' . . . means any byproduct, which results from heating the drug(s) and is not responsible for producing a therapeutic effect.") and Paragraph [0099] ("'Heat stable drug' refers to a drug that has a TSR $\geq$9 when vaporized from a film of some thickness between 0.05 μm and 20 μm.").

Anticipation requires that "a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." *PPG Industries. Inc. v. Guardian*

Industries Corp., 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1642 (Fed. Cir. 1996), *see also* MPEP §2131 citing *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051 (Fed. Cir. 1987). As Byron et al. fails to disclose a thin film of a drug composition comprising a heat stable drug, heating such a drug composition to produce a vapor, or obtaining a condensation aerosol comprising particles characterized by less than 10% drug degradation products by weight the reference can not be said to anticipate the kit of Claim 74. As Claims 75, 76 and 78-82 depend from Claim 74, Claims 75, 76 and 78-82 are not anticipated for the same reasons. Applicants have canceled Claim 77 as its limitations have been incorporated into Claim 74. Accordingly, the Applicants respectfully request that the Examiner reconsider and withdraw the rejection of these claims under 35 U.S.C §102(e).

The Rejection under 35 U.S.C. §103(a)

The Examiner rejected Claims 20-82 under 35 U.S.C. §103(a) as being unpatentable over Byron (20040016427 A1) in view of Bartus et al. (6,514,482). In support of this rejection, the Office Action states that Byron et al. lacks "specific disclosure on medicaments" but that "Bartus teaches a method of pulmonary delivery of a medicament, which includes administering . . . particles . . . , where the particles preferably have an aerodynamic diameter between about 1 and 5 μm." Office Action at 3. The Office Action further states that Bartus discloses medicaments containing from 1 to about 90 weight percent of drugs, including migraine treating agents such as NSAIDs, triptans, isometheptene mecate, etc., that are delivered via a dry powder inhaler, metered dose inhaler, nebulizer or instillation techniques. *Id.* at 3-4.

The Office Action states that Bartus lacks "teachings on specific steps in producing condensation aerosol and also lacks specific disclosure on the presence of less than 5% degradation products." *Id.* at 3-4. However, the Office Action asserts that it "would have been obvious to a person of ordinary skill in the art at the time the invention was made to have implemented the medicaments of Bartus et al. in the aerosol device of Byron et al. for delivering the aerosolized compositions to a subject's respiratory tract because it would be desirable to provide a wide variety of therapeutic agents in an aerosol delivery article which is capable of producing the condensate aerosol particles of relatively small size without the necessity of subjecting the material to be aerosolized to exposure to significant heat or high temperatures. *Id.* at 4.

Applicants respectfully disagree. One of skill in the art seeking to prepare and administer aerosolized compositions for delivery to a subject's respiratory tract without exposure to significant heating or high temperatures would not have to look beyond the disclosure of Bartus. Moreover, Bartus does not teach that small particles are desirable. To the contrary, Bartus states that larger, low density particles aerosolize more efficiently and avoid phagocytic engulfment by alveolar macrophages more effectively than smaller, denser aerosol particles. Bartus col. 13, lines 61-64.

"The aerodynamic diameter can be calculated to provide for maximum deposition within the lungs. Previously this was achieved by the use of very small particles of less than about five microns in diameter, preferably between about one to about three microns, which are then subject to phagocytosis. Selection of particles which have a larger diameter, but which are sufficiently light (hence the characterization "aerodynamically light"), results in an equivalent delivery to the lungs, but the larger size particles are not phagocytosed. Improved delivery can be obtained by using particles with a rough or uneven surface relative to those with a smooth surface" (Bartus col. 13, line 65 to col. 14, line 7).

As pointed out in the Office Action, the aerosols generated by the device of Byron et al. typically have a mass median particle diameter of less than 2 microns, while Bartus teaches that the preferred size range of particles is at least about 5 microns, preferably between about 5 microns and 30 microns. See, e.g., Bartus at col. 12, lines 60-66; col. 14, lines 12-14. Thus, Bartus teaches away from delivering its compositions using the device of Byron et al.

Moreover, one of skill in the art would not have a reasonable expectation that the device of Byron et al. would successfully form condensation aerosols suitable for inhalation that are characterized by less than 10% drug degradation products and an MMAD of less than 5 microns from the compositions of Bartus. For instance, under the method of Byron et al., the compositions of Bartus ("solid component") would have to be put into liquid form by combining with a "liquid component." Byron et al., paragraph [0076]. However, Byron et al. fails to provide specific guidelines for selecting an appropriate "liquid component" for a given drug ("solid component") or for predicting what effect heating the mixture will have on the solid component. This is further complicated when the solid component contains one or more additional component in addition to the drug, such as the surfactants, phospholipids, amino acids, etc., taught in Bartus. Bartus, col. 8, lines 42 to col. 11, line 53.

Finally, these references do not teach or suggest all of the elements of independent Claim 74. Neither Bartus nor Byron et al. teaches or discloses a thin film of a drug composition comprising a drug, on a solid support, or heating such a drug composition to produce a vapor. Furthermore, like Byron et al., Bartus lacks specific disclosure on a heat stable drug or a condensation aerosol comprising particles characterized by less than 10% drug degradation products as those terms are used with respect to the present invention.

Thus, these references singly or in combination do not teach or suggest all the claim elements, but rather teach away from the claimed invention. Accordingly, the Office Action fails to establish even a *prima facie* case of obviousness. Moreover for the same reason, there would be no motivation to combine the references to achieve the presently claimed invention, nor is it seen how the combination of the references

would achieve the presently claimed invention. Claims 75, 76 and 78-82 which depend from Claim 74 are not obvious for the same reasons as Claim 74.

Finally, the Examiner rejected Claims 20-82 under 35 U.S.C. §103(a) as being unpatentable over Faithfull et al. (6,041,777) in view of Bartus et al. (6,514,482). In support of this rejection, the Office Action states in summary that Faithfull teaches methods and apparatus for closed-circuit ventilation therapy, including the use of nebulizers to provide fluorochemicals and/or pharmaceutical agents, heated above body temperature, to a ventilating gas in the form of a vapor and that this is accomplished by spraying or contacting a wetted surface or wick with the gas to form droplets. *Id.* at 5. The Office Action states that Faithful also discloses that the method provides for the independent delivery of pharmaceutical agents or their use in conjunction with other vapors.

The Office action states that Faithfull lacks "disclosure on medicaments" but that Bartus "discloses a wide variety of therapeutic agents suitable for aerosol delivery." *Id.* at 5. The Office Action asserts that it "would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the method and apparatus for ventilation therapy as taught by Faithfull by adding the wide variety of medicaments suitable for aerosol delivery as taught by Bartus, because of the disclosed benefits of such a method, including minimized trauma to the lungs and a better resolution of pulmonary and systemic disorders, and because of the need to treat a wide variety of diseases." *Id.* at 5-6.

Applicants respectfully disagree in view of the elements of the pending claims and the disclosures of Bartus and Faithfull. Bartus fails to teach or disclose a condensation aerosol. Rather Bartus is directed to a method of delivering low tap density particles for the treatment of CNS disorders and in particular, Parkinson's disease, via dry power inhalers or metered dose inhalers. Nowhere does Bartus disclose or suggest condensing a vapor to form a condensation aerosol comprising a drug, nor the advantages obtained by such a condensate aerosol. Additionally, Bartus lacks teachings on heating the drug composition. Dry powder inhalers, metered dose inhalers, nebulizers or instillation techniques do not vaporize the drug and then form a condensate of the drug. Additionally, in Bartus there is no disclosure of how one would form such a condensation aerosol comprising an antiparkinsonian drug or any other drug compound to generate an aerosol comprising particles characterized by less than 10% drug degradation products by weight, or how to obtain aerosols having a MMAD of less than 5 microns when heating a drug composition to produce a vapor and condensing the vapor. Nor does Bartus disclose a thin layer of a drug composition comprising a drug, on a solid support. These elements, which are not taught in Bartus, are required by independent Claim 74.

Faithfull does not cure these deficiencies or make obvious in view of Bartus how to accomplish these tasks. Faithfull does not disclose or teach a condensation aerosol as defined by the Applicants' claims (or any condensation aerosol for that matter) or how to make such an aerosol. Faithfull discloses

the use of a warmed fluorochemical as a solvent for delivering the active compound "oxygen" to the lungs of the patient using a ventilation system. The active or therapeutic compound or drug in Faithfull is not heated to produce a vapor or condensed to form a condensation aerosol comprising particles, as is set forth in Claim 74 of the present application. Instead, Faithfull requires the use of a wetted surface or wick to get the fluorochemical (solvent) to form a droplet. Moreover, as is stated in the Office Action, the fluorochemical in the Faithfull reference, unlike the present invention, is being delivered to the lung as a vapor and not an aerosol. See Office Action at 4 ("As the fluorochemical **vapor** cools in the body it is deposited on the pulmonary surfaces" (emphasis added)). Faithfull does not disclose how to make a condensation aerosol comprising particles characterized by less than 10% drug degradation products by weight, or how to obtain a condensation aerosol having an MMAD of less than 5 microns. Nor does Faithfull teach or disclose a thin film of a drug composition comprising a drug, on a solid support, or heating such a drug composition to produce a vapor.

The Office Action suggests that condensates by their nature have a high percentage of purity of the drug and less degradation products. Applicants respectfully disagree. The mere fact that an aerosol is formed by condensation does not mean that the aerosol will have a high percentage of drug and less degradation products.

According to the MPEP § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations." Obviousness cannot be established by combining teachings in the prior art, absent some teaching or suggestion in the prior art that the combination be made (*In re Stencel* 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987); *In re Newell* 891 F. 2d 899, 13 USPQ2d 1248 (Fed. Cir. 1989)).

Faithfull does not cure the deficiencies of Bartus. Accordingly, the Office Action fails to establish even a *prima facie* case of obviousness as each and every element of the invention is not taught or disclosed by these references. Moreover, there would be no motivation to combine the references to achieve the presently claimed invention. Even if the cited references were combined, the claimed invention would not result because neither Bartus nor Faithfull is directed to a thin film of a drug composition comprising a drug, on a solid support, or heating such a drug composition to produce a vapor, or to forming condensation aerosols comprising particles characterized by less than 10% drug degradation products and an MMAD of less than 5 microns. Claims 75, 76 and 78-82 which depend from Claim 74 patentably define over Bartus and Faithfull for the same reasons as Claim 74.

Accordingly, and in light of the foregoing arguments, the Applicants respectfully submit that these amendments put the case in condition for allowance and request that the Examiner reconsider and withdraw all rejections based on 35 U.S.C §103.

Double Patenting

Claims 1-82 were rejected under the judicially created doctrine of obviousness-type double patent as being unpatentable over claims of U.S. Patent Nos. 6,716,415; 6,716,416; 6,716,417; 6,737,042; 6,737,043; 6,740,307; 6,740,308; 6,740,309; 6,743,415; 6,759,029; 6,776,978; 6,780,399; 6,780,400; 6,783,753; 6,797,259; 6,803,031; 6,805,853; 6,805,854; 6,814,955 and 6,855,310 as these claims are "either anticipated by, or would have been obvious over, the reference claims." Office Action at 6-7. Also, Claims 1-82 were provisionally rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application Nos. 10/151,626; 10/302,010; 10/437,643; 10/442,385; 10/696,959; 10/712,365; 10/719,763; 10/719,899; 10/734,902; 10/735,198; 10/735,199; 10/735,495; 10/735,496; 10/735,497; 10/749,535; 10/749,536; 10/749,783; 10/750,303; 10/766,149; 10/766,279; 10/766,566; 10/766,574; 10/766,634; 10/766,647; 10/767,115; 10/768,205; 10/768,220; 10/768,281; 10/768,293; 10/769,046; 10/769,051; 10/769,157; 10/769,197; 10/775,583; 10/775,586; 10/791,915; 10/792,001; 10/792,012; 10/792,013; 10/792,096; 10/792,239; 10/813,721; 10/813,722; 10/814,690; 10/814,998; 10/815,527; 10/816,407; 10/816,492 and 10/816,567. *Id.* at 7-9.*

Applicants have filed with this response Terminal Disclaimers with regard to U.S. Patent Nos. 6,716,415; 6,716,416; 6,716,417; 6,737,042; 6,737,043; 6,740,307; 6,740,308; 6,740,309; 6,743,415; 6,759,029; 6,776,978; 6,780,399; 6,780,400; 6,783,753; 6,797,259; 6,803,031; 6,805,853; 6,805,854; 6,814,955 and 6,855,310 and copending Application Nos. 10/151,626; 10/302,010; 10/437,643; 10/442,385; 10/696,959; 10/712,365; 10/719,763; 10/719,899; 10/734,902; 10/735,198; 10/735,199; 10/735,495; 10/735,496; 10/735,497; 10/749,535; 10/749,536; 10/749,783; 10/750,303; 10/766,149; 10/766,279; 10/766,566; 10/766,574; 10/766,634; 10/766,647; 10/767,115; 10/768,205; 10/768,220; 10/768,281; 10/768,293; 10/769,046; 10/769,051; 10/769,157; 10/769,197; 10/775,583; 10/775,586; 10/791,915; 10/792,001; 10/792,012; 10/792,013; 10/792,096; 10/792,239; 10/813,721; 10/813,722; 10/814,690; 10/814,998; 10/815,527; 10/816,407; 10/816,492 and 10/816,567. Applicants believe that this addresses the Examiner's concerns and respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of these actions and remarks.

Conclusion

The Applicants appreciate the Examiner's careful and thorough review of the application and submit that the Examiner's concerns have been addressed by the amendments and remarks above. The Applicants accordingly request the Examiner to withdraw all rejections and allow the application. In the event the Examiner believes a telephonic discussion would expedite allowance or help to resolve outstanding issues, prosecution of the application, then the Examiner is invited to call the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date: September 8, 2005

Darla G. Yoerg, #48,053
Swanson & Bratschun, L.L.C.
1745 Shea Center Drive, Suite 330
Highlands Ranch, Colorado 80129
Telephone: (303) 268-0066
Facsimile: (303) 268-0065

S:\CLIENTFOLDERS\ALEXZA\30.03CON\00030.03CON RESP OA-ART.DOC

* The publication number corresponding to the present application (i.e., 20040099269), although appearing in the list set forth in the Office Action, is not included here.